

REMARKS/ARGUMENTS

Claims 1-16 are pending in the instant application. In order to expedite prosecution Applicants have amended claim 1. The following remarks are believed to be fully responsive to the Office Action.

Claim Rejections – 35 USC § 102

Claims 1, 6, 10, 11, 13 and 14 stand rejected under 35 USC §102(b) as being anticipated by deLearie (US 5,508,388). Applicants have amended claim 1 to read on the molar amount of pyridine being equal to or less than 4 times the molar amount of DTPA. Support for the amendment in claim 1 can be found on page 3, line 23 of the application as published (WO2005/058846).

In view of the Examiner's points 5 -7 made on pages 2-3 of the Office Action dated February 28, 2008 ("Office Action"), Applicants now believe that claims 1, 6, 10, 11, 13, and 14 are in condition for allowance and respectfully request that the Examiner's rejections for claims 1, 6, 10, 11, 13, 14 under 35 USC §102 (b) be withdrawn.

The same argumentation also applies to claim 17 which is previously withdrawn from consideration.

Claim Rejections – 35 USC § 103(a)

Claims 1, 6 – 11 and 13 - 15 stand rejected under 35 USC 103(a) as being unpatentable over Dazzi (US 3,660,388) in view of deLearie et al (US 5,508,388).

Applicants were aware of the technology described by Dazzi prior to the present invention and directs the Examiner's attention to page 1, lines 20 to 27 of the description in

the present application (published international application WO 2005/058846). Applicants therefore fully agree with the Examiner that at the time of the invention it was obvious to one ordinarily skilled in the art to utilize acetic anhydride and pyridine in the process for the production of DTPA-bis(anhydride) without the use of acetonitrile. As the Examiner notes, Dazzi does not disclose less than 6.5 moles of pyridine per mole of DTPA. Applicants has surprisingly found that it was possible to reduce the amount of pyridine beyond the amount that Dazzi teaches and avoiding the use of acetonitrile, while at the same time maintaining a high yield, see p. 2, lines 14 to 28.

The Examiner holds that deLearie discloses that by minimizing the amount of pyridine (to 4.5 eq.) in the reaction mixture, the amount of time necessary for the reaction can be reduced from 48h (Dazzi) to 18-22h. The Examiner further holds that it would be obvious to reduce the amount of pyridine to reduce the toxicity while also reducing the reaction time without the use of acetonitrile.

Applicants respectfully disagree with the Examiner's assertions of the teaching of deLearie.

deLearie in Example 2, with the heading "Effect of Temperature and Acetonitrile on the Preparation of DTPA-bis(anhydride)" refers to a series of experiments wherein in the first set apparently does not indicate use of acetonitrile (col. 6, lines 11 to 18) and varies the temperature of the reaction mixture between 55 to 74°C by using an oil-bath. The reactions were performed for 18-22 hours.

The second set of experiments (col. 6, lines 18 to 20) was performed in with acetonitrile was used as a diluent in the preparation.

deLearie discloses (col. 6, lines 21 to 29) that he determined the results of the reaction, i.e. the completion of the reaction and the quality of the produced anhydride, but does not provide any data.

deLearie therefore does not disclose the amount of DTPA-bis(anhydride) that was formed during the reaction time of 18-22 hours with or without acetonitrile in Example 2, i.e. deLearie is silent about the yield in Example 2. In Example 3, deLearie discloses the effect of the reaction time and notes >99% completion of the reaction after 18 and 22 hours and concludes that DTPA-bis(anhydride) was best prepared overnight. There is however no indication that deLearie repeated the first set of experiments of Example 2 (with no addition of acetonitrile) in Example 3. At the end of Example 2, deLearie concludes that DTPA-bis(anhydride) was best prepared with acetonitrile, and that he in Example 3 refers back to Example 1 where the reaction mixture contains acetonitrile.

One skilled in the art would therefore understand that the experiments in Example 3 are run with the addition of acetonitrile. Therefore, deLearie does not disclose that a reaction time of 18-22 hours yields any DTPA-bis(anhydride) at all, let alone an acceptable yield of DTPA-bis(anhydride).

Applicants therefore find that deLearie in no way teaches one skilled in the art that the reaction time can be reduced from 48h (Dazzi) to 18-22h by employing the teaching of deLearie, and that it would in no way be obvious to reduce the amount of pyridine to reduce the toxicity while also reducing the reaction time without the use of acetonitrile as held by the Examiner in points 11-15 of the instant Office Action..

Applicants understands Examiner's assertions in point 16 of the Office Action to mean that it would be obvious to vary and/or optimize the amounts of the constituents in the reaction mixture, based on In re Aller "[W]here the general conditions of a claim is disclosed in the prior art, it is not inventive to discover optimum or workable ranges by routine experimentation." Applicant will point out that although Dazzi utilize acetic anhydride and pyridine in the process for the production of DTPA-bis(anhydride) without the use of acetonitrile, Dazzi does not disclose less than 6.5 moles of pyridine per mole of DTPA. deLearie on the other hand concludes (col. 6, lines 30 to 35) that "[B]ased upon the result, it

was concluded that DTPA-bis(anhydride) was best prepared between 55 to 65°C with 0.5 ml acetonitrile per gram DTPA used in the reaction”. Hence, deLearie et al teaches away from performing the reaction with an amount of 4.5 mole pyridine without addition of acetonitrile. Hence, the present invention involves an inventive effort and the Applicants had to overcome the prejudice created by deLearie that it was not possible to reduce the amount of pyridine in the instant production process of DTPA-bis(anhydride) beyond the level taught by Dazzi.

Claims 1, 6 – 11 and 13 - 15 are further rejected under 35 USC 103(a) as being unpatentable over Gibby (US 4,822,594) in view of deLearie et al et al (US 5,508,388).

Applicants were aware of the technology described by Gibby prior to the present invention and direct the Examiner’s attention to page 1, lines 29 to 32 of the description in the present application (published international application WO 2005/058846). Applicants therefore concur with the Examiner that at the time of the invention it was obvious to one ordinarily skilled in the art to produce DTPA-bis(anhydride) by reacting DTPA with a molar amount of anhydrous acetic acid four times that of DTPA and a molar amount of pyridine that is 6.2 times that of DTPA at 65°C for 20h without the use of acetonitrile as disclosed in col. 4, Example 1. Applicants has surprisingly found that is was possible to reduce the amount of pyridine beyond the amount that Gibby teaches and avoiding the use of acetonitrile, while at the same time maintaining a high yield, see p. 2, lines 14 to 28.

Applicants will point out that the amount of pyridine in Example 1 of Gibby is calculated to be 6.2 as follows:

80 grams DTPA corresponds to 0.20 mmole DTPA (MW 393.35)

100ml anhydrous pyridine corresponds to 98grams which corresponds to 1.24 mmole pyridine (MW 79.1)

76ml acetic anhydride corresponds to 82 grams which corresponds to 0.80 mmole acetic anhydride (MW 102.9)

Molar ratio DTPA : acetic anhydride : pyridine is $0.20 : 0.80 : 1.24 = 1.0 : 4.0 : 6.2$.

Applicants understand that the Examiner holds that deLearie discloses production of DTPA-bis(anhydride) by reacting DTPA with acetic anhydride (not acetic acid) and pyridine in the molar ratio of 1.0 : 3.0 : 4.5 between 55 to 74°C for 18-22h without addition of acetonitrile. The Examiner holds that deLearie discloses that by minimizing the amount of pyridine (to 4.5 eq.) in the reaction mixture, the amount of time necessary for the reaction can be reduced from 20h (Gibby) to 18h. The Examiner further holds that it would be obvious to reduce the amount of pyridine to reduce the toxicity while also reducing the reaction time without the use of acetonitrile.

Applicants respectfully disagree to these assertions of the teaching of deLearie. Applicants interpretation of the teachings of deLearie is provided under the discussion of Dazzi/deLearie above.

Applicants therefore find that deLearie in no way teaches one skilled in the art the reaction time can be reduced from 20h (Dazzi) to 18h by employing the teaching of deLearie, and that it would in no way be obvious to reduce the amount of pyridine to reduce the toxicity while also reducing the reaction time without the use of acetonitrile as held by the Examiner in points 17 – 20 of the instant Office Action.

Regarding the Examiner's assertions in point 21, Applicants refer to the arguments put forward above as response to Examiner's arguments under point 16 of the instant Office Action. Applicants will point out that although Gibby utilize anhydrous acetic acid and pyridine in the process for the production of DTPA-bis(anhydride) without the use of acetonitrile, Gibby does not disclose less than 6.2 moles of pyridine per mole of DTPA. deLearie on the other hand concludes (col. 6, lines 30 to 35) that "[B]ased upon the result, it was concluded that DTPA-bis(anhydride) was best prepared between 55 to 65°C with 0.5 ml acetonitrile per gram DTPA used in the reaction". Hence, deLearie teaches away from performing the reaction with an amount of 4.5 mole pyridine without addition of acetonitrile. Therefore, the present invention involves an inventive effort and the Applicants had to overcome the prejudice created by deLearie et al that it was not possible to reduce the

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amount of pyridine in the instant production process of DTPA-bis(anhydride) beyond the level taught by Gibby.

Applicants now believe that claims 1, 6-11, and 13-15 are in condition for allowance and respectfully request that the Examiner's rejections for these claims under 35 USC §103 (a) be withdrawn.

CONCLUSION

In view of the amendments and remarks herein, Applicants believe that each ground for rejection made in the present application has been successfully overcome, and that all the pending claims, 1-16, are in condition for allowance.

The Examiner is invited to telephone the undersigned in order to resolve any issues that might arise and to promote the efficient examination of the current application.

Respectfully submitted,

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